

## Lupus Nephritis in the Era of Biomarkers

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*Clin J Am Soc Nephrol* 11: 4–5, 2016. doi: 10.2215/CJN.12371115

Renal biopsy remains the standard of care for the evaluation of suspected flares in lupus nephritis (1) and is generally indicated when proteinuria, active urine sediment, or elevated serum creatinine is present. By the time that a patient presents with these features, injury induced by the lupus disease activity may already be present, including acute and more concerning, chronic changes. Renal biopsy carries a small but significant risk, primarily of bleeding resulting in perirenal hematoma, blood transfusion, and in patients with severe (although rare) cases, need for angiogram (2). In light of difficulty in predicting kidney damage clinically or using current laboratory parameters (plus the inherent risk of kidney biopsy), the search for useful biomarkers continues; the goal of the ideal biomarker is to warn of impending disease, allow for more accurate prediction of lupus-related renal histopathology, and allow for monitoring of changes in disease activity.

For a biomarker to be reliable and useful in clinical practice, it should have the following characteristics: it should have biologic and pathophysiologic relevance, it must be easy to use for routine practice, and it must accurately reflect disease state and track changes in disease activity (3). Although there have been several biomarkers identified in lupus nephritis, none have sufficiently fulfilled these criteria. Although anti-double-stranded DNA antibodies and complement levels have long been recognized as pathophysiologic contributors and predictors of disease activity, their ability to accurately predict flares or histopathology is limited. Anti-C1q antibodies have been associated with lupus nephritis, but the ability of this antibody to track disease or predict histopathology has not been shown (4). Other biomarkers, such as uMCP-1 and uIL-8, have also shown insufficient predictive ability (5). However, some have shown improvement in the diagnostic accuracy through the use of a combination of biomarkers (6). Although it is likely that, in the future, a scoring system using combined markers will become useful, it currently remains elusive. In this context, the discovery of new biomarkers is a high priority.

The nephrology world has witnessed a fast-growing interest in biomarkers associated with renal disease. New biomarkers with potential clinical utility have been identified in both AKI and CKD (7). Moreover, the Food and Drug Administration has recently approved the use of a bedside urine test identifying the presence of two cell cycle arrest proteins (IGF binding protein 7 and tissue inhibitor of metalloproteinases), the product

of which correlates with risk of developing AKI (8). Although the clinical utility of these biomarkers remains ill defined at this time, it does suggest a coming of age of biomarkers in AKI that will likely spread to other areas of nephrology, including lupus nephritis.

In this issue of the *Clinical Journal of the American Society of Nephrology*, Birmingham *et al.* (9) describe a subset of patients with lupus and a very specific antibody (anti-C3b IgG) for lupus nephritis. The study was carried out among 114 patients with SLE followed bi-monthly in the prospective Ohio SLE Study cohort: 73 with lupus nephritis and 41 without history of nephritis. Patients without lupus were also available to serve as normal controls. Searching for a biologically and pathophysiologically relevant biomarker, Birmingham *et al.* (9) measured antibodies against several complement proteins, including those to C1s, C4b, C2, C3b, C1INH, FH, C4BP, and FI in this observational cohort. Birmingham *et al.* (9) then performed two analyses; one was a cross-sectional analysis at the time of enrollment to assess association with disease, and one was a longitudinal analysis to assess ability of antibodies to predict a lupus flare.

To screen for disease-associated antibodies, the profiles of the aforementioned antibodies in eight patients with lupus nephritis were compared with those in five control patients without lupus. Only anti-C3b IgG antibody showed a significant difference between lupus nephritis and normal samples. This antibody in addition to anti-C1q, an already established biomarker (although not previously studied through serial measurements), were, therefore, chosen for additional study as a potential biomarker of lupus nephritis and a predictor of flares.

Cross-sectional analysis was carried out comparing antibody profiles (at time of cohort entry) of 114 cohort patients with those of 40 nonlupus controls. The analysis showed that both anti-C3b and anti-C1q were associated with SLE (compared with normal controls) and lupus nephritis in those with SLE. Of note, 26 of 27 patients with anti-C3b IgG were also positive for anti-C1q IgG. Anti-C3b was less (and poorly) sensitive for lupus nephritis compared with anti-C1q (36% versus 63%) but highly specific for its presence (98% versus 71%) compared with anti-C1q. Furthermore, anti-double-stranded DNA antibodies were similarly sensitive to those of anti-C3b but less specific for lupus nephritis. Finally, those developing a flare were more likely ( $P < 0.01$ ) to have anti-C3b antibodies (51%) than those

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who did not develop a flare (19%); there was no difference in proportions of anti-C1q positivity.

In the longitudinal analysis, anti-C1q IgG and anti-C3b IgG were measured every 2 months before diagnosis of a flare. Lupus nephritis flares were defined on the basis of serum creatinine, proteinuria, and urine sediment similar to current American College of Rheumatology criteria and not on the basis of findings on kidney biopsy. Anti-C3b and anti-C1q antibody changes over time did not associate with a flare; however, in those who had anti-C3b antibodies, anti-C1q antibody levels at the time of lupus flare showed significant elevation compared with 4 and 6 months before lupus nephritis flare. There seemed to be no difference in those who were anti-C3b negative. Anti-C3b antibodies themselves were not significantly elevated at the time of flare, although there was a trend for increase ( $P=0.07$ ).

Birmingham *et al.* (9) note that, as expected, C3 levels were inversely correlated with anti-C3b antibodies, and they suggest that C3b neoepitopes forming at sites of kidney damage may be driving the formation of anti-C3b antibodies. Birmingham *et al.* (9) also appropriately argue that this study suggests other indicators of complement activation that may have clinical use in the management of lupus nephritis.

This study carries several major limitations. Most importantly, flares are described using only clinical parameters without a kidney biopsy, the current gold standard for determination of renal flare, and there are no outcome data on those whose flare was predicted by the antibody presence or changes. The limited ability of clinical features to predict histopathology is well described (10). Therefore, in the absence of histopathology, which will have a significant effect on outcome, it is difficult to determine what effect such antibodies may have in the care of patients with lupus. In addition, the study included a relatively small number of patients, in whom only a minority of patients with lupus possess the anti-3b antibodies (27 of 114 in the cohort).

These limitations, although significant, should not detract from the importance of this study. Birmingham *et al.* (9) have defined a novel biomarker, which has biologic and pathophysiologic relevance, with potential for disease prediction. The high specificity of anti-C3b may allow for greater suspicion for renal disease in the small subset of patients who possess it and therefore, encourages closer monitoring for renal involvement in such patients. However, before using such an antibody in clinical practice, additional studies that include kidney biopsies and renal outcomes will need to be carried out. Although use of these antibodies as a predictor of the presence or future risk of lupus nephritis will fulfill the ease of use criterion of an effective biomarker, the tracking of disease over time is less simple, because it may require a combination of biomarkers (anti-C1q levels and/or other biomarkers in those already positive for anti-C3b) with cutoffs that would require specific definitions. Only additional study will determine if these antibody parameters will be sufficiently accurate and sensitive in detecting presence or changes in disease activity (or histopathology).

This study raises interesting diagnostic and therapeutic questions. Will biomarkers that predict lupus nephritis lead

to early renal biopsy? Will this lead to increased rates in induction of remission given earlier therapy? Ultimately, will the presence of effective biomarkers allow for avoidance of potentially dangerous kidney biopsies or effective empirical treatment in those who have contraindications to biopsy? This study adds to our current understanding and moves us a little closer to answering these important questions.

#### Disclosures

None.

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Published online ahead of print. Publication date available at [www.cjasn.org](http://www.cjasn.org).

See related article, “Relationship of Circulating Anti-C3b and Anti-C1q IgG to Lupus Nephritis and Its Flare,” on pages 47–53.